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| EXAMINER | |
|---|---|
| LANDSMAN, ROBERT S | |

| ART UNIT | PAPER NUMBER |
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| 1647 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

INFO@ORTPATENT.COM

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/576,995 | HUI, MIZHOU | |
| | Examiner | Art Unit | |
| | Robert Landsman | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *22-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/23/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

***1. Formal Matters***

A. In the Election filed 5/22/09, Applicants elected (a) TNF neutralizer domain, (b) the extracellular domain for TNFR and (c), TNFR of TNFRII, which all make up SEQ ID NO:2.

B. Claims 1-21, 25 and 26 are the subject of this Office Action.

***2. Specification***

A. Though the Figures have been accepted, it is noted that much of Figures 1 and 2 and part of Figure 3 are not visible. However, if the application is passed to issue, the submission of Formal Drawings should remedy the situation.

B. The title has been amended to remove the term "Novel" since all patents claim novel subject matter. Applicants may suggest a new title if they desire.

C. Though none could be found, Applicant is advised that embedded hyperlinks and/or other forms of browser-executable code are impermissible and require deletion. The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference.

D. Though none could be found, trademarks should be capitalized wherever they appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

E. Though none could be found, any U.S. or Foreign Applications cited in the specification which have since issued should be updated with the corresponding Patent No.

F. Though none issues could be found, according to 37 CFR 1.821(d) (MPEP § 2422), where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

***3. Claim Objections***

A. Claim 19 is objected to since "TNF' and "IL-1" should be hyphenated.

***4. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 6, 7 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while then being enabling for chimeric proteins comprising the domains recited in claim 1, does not reasonably provide enablement for "functional equivalents" of these domains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 6, 10 and 11 (and dependent claims 7 and 12) recite "functional equivalents". The breadth is excessive with regard to any functional equivalent to a TNF neutralizer domain, a dimerization domain and an IL-1 receptor antagonist domain. The specification only provides guidance and working examples of SEQ ID NO:2 which comprises the full-length TNF neutralizer domain, full-length IL-1ra domain and the disclosed dimerization domain. "Functional equivalents" would have one or more amino acid

substitutions, deletions, insertions and/or additions to these domains, including that of SEQ ID NO:2. It is not predictable to one of ordinary skill in the art how to make these functional domains other than the full-length domains disclosed in the specification.

These factors lead the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

B. Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while then being enabling for the chimeric proteins of claim 1, does not reasonably provide enablement for methods of treating a TNF- and IL-1-dependent disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The breadth of the claims is excessive. The claims are drawn to treating any TNF- and IL-1-related disorder. Claim 21 is limited to arthritis and psoriasis. However, the specification does not provide any guidance or working examples that the claimed chimeric proteins used in the rejected method claims is able to treat any disease. It appears that Figure 9 only shows a shift in potency. However, since the shift is "to the right" it appears that the THFRII-Fc-IL-1ra chimera is less potent. Furthermore, there is no added effect on the maximum response using the chimera. Figure 8 has similar issues except that there appears to be no difference between the two compositions. In addition, Table 3 does not compare IL-1ra as a control so it cannot be determined that the chimera is more effective than IL-1ra alone.

Furthermore, in the examples, Applicants use the full-length TNFR and IL-1a proteins. However, the claims are drawn towards using only the neutralizer and receptor antagonist domains, which have not been used in any Examples. Therefore, the smallest functional domains cannot be determined. In other words, as seen in paragraph A in the above rejection under 35 USC 112, first paragraph, only the full-length proteins were shown to be effective. It is noted that these Examples only demonstrate in vitro work and even if Applicants amended their claims to recite using only the full-length proteins, this in itself would not obviate the rejection. Finally, it is not predictable to one of ordinary skill in the art how to

make a functional chimera using less than the full-length proteins for in vivo use of treating any and all TNF- or IL-1-related diseases.

These factors lead the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

***5. Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 6, 7 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The acronym "IL-1ra should be spelled out upon first use. It is suggested that the abbreviation be added to claim 1, part (2).

***6. Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 1-11, 13-21, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (reference AQ on the 1449 filed 6/23/08) in view of Gilles et al. (U.S. 6,617,135). The claims recite a chimeric polypeptide comprising a TNF neutralizer domain, an IL-1ra domain and a dimerization domain where the domains are operably linked.

Applicants disclose on page 2 of the specification that an Immunex clinical trial showed that the use of soluble TNFRII and IL-1ra led to a higher incidence of infection that when given separately.

However, the art seems mixed as Kim et al. teach that IL-1ra and soluble TNFR (which would comprise the TNF neutralizing domain) provided a synergistic therapeutic effect in antigen-induced arthritis.

Kim et al. do not teach the use of a dimerization domain in the TNFR/IL-1ra fusion. However, Gilles et al. do teach the use of an Fc dimerization domain to fuse two cytokines (column 15, lines 35-38 and column 18, lines 46-48). It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have used the dimerization domain of Gilles et al. in the fusion protein of Kim et al. since the IL-1ra and TNFR of Kim et al. are both cytokine receptors and Gilles et al. teach the fusion of cytokines with Fc. Dimerization of these two cytokine receptors increases the chance of in vivo receptor/ligand binding.

B. Claims 1-11, 13-21, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghivizzani et al. (reference AR on the 1449 filed 6/23/08) in view of Gilles et al. (U.S. 6,617,135). The claims recite a chimeric polypeptide comprising a TNF neutralizer domain, an IL-1ra domain and a dimerization domain where the domains are operably linked.

Applicants disclose on page 2 of the specification that an Immunex clinical trial showed that the use of soluble TNFRII and IL-1ra led to a higher incidence of infection that when given separately. However, the art seems mixed as Ghivizzani et al. teach that full-length IL-1 (which would comprise the antagonist domain) and full-length soluble TNFR (which would comprise the TNF neutralizing domain) provided a synergistic therapeutic effect in experimental arthritis. Ghivizzani et al. use IL-1 receptor fusion together with a soluble TNFR fusion (Abstract).

Ghivizzani et al. do not teach the use of a dimerization domain in the TNFR/IL-1ra fusion. However, Gilles et al. do teach the use of an Fc dimerization domain to fuse two cytokines (column 15, lines 35-38 and column 18, lines 46-48). It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have used the dimerization domain of Gilles et al. in the fusion protein of Ghivizzani et al. since the IL-1ra and TNFR of Kim et al. are both cytokine receptors and Gilles et al. teach the fusion of cytokines with Fc. Dimerization of these two cytokine receptors increases the chance of in vivo receptor/ligand binding.

C. Claims 1-11, 13-21, 25 and 26 are rejected over Smith (US 20060275868) in view of Gilles et al. (U.S. 6,617,135). The claims recite a chimeric polypeptide comprising a TNF neutralizer domain, an IL-1ra domain and a dimerization domain where the domains are operably linked.

Applicants disclose on page 2 of the specification that an Immunex clinical trial showed that the use of soluble TNFRII and IL-1ra led to a higher incidence of infection that when given separately. However, the art seems mixed as Smith teaches that full-length IL-1 (which would comprise the antagonist domain) and full-length TNFR (which would comprise the TNF neutralizing domain) can be used to treat arthritis ([0090], [0091] and [0092]).

Smith does not teach the use of a dimerization domain in the TNFR/IL-1ra fusion. However, Gilles et al. do teach the use of an Fc dimerization domain to fuse two cytokines (column 15, lines 35-38 and column 18, lines 46-48). It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have used the dimerization domain of Gilles et al. in the fusion protein of Smith since the IL-1ra and TNFR of Kim et al. are both cytokine receptors and Gilles et al. teach the fusion of cytokines with Fc. Dimerization of these two cytokine receptors increases the chance of in vivo receptor/ligand binding.

***7. Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ormum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

A. Claims 1-21, 25 and 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 10, 13, 14, 15, 17 and 19-22 of copending Application No. 11/576,963. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite a chimeric or fusion protein comprising a TNFR and an IL-1ra which can dimerize (see especially claims 2, 10 and 15 of the '963 application). Both applications also claim vectors and host cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

B. Claims 1-21, 25 and 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 12-16, 18 and 20-24 of copending Application No. 11/996,816. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a TNFR/IL-1ra fusion which also comprises a dimerization domain. The claims of the '916 application recite a fusion comprising two biologically active proteins and a dimerization domain (see especially claims 1 and 12). Since TNFR and IL-1ra are both biologically active proteins the genus of fusion proteins of the '816 application is anticipated by the species of TNFR and IL1ra fusion of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***8. Conclusion***

A. No claim is allowable.

***Advisory information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman, Ph.D. whose telephone number is (571) 272-0888. The examiner can normally be reached on M-F 10 AM – 6:30 PM (eastern).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Robert Landsman/
Primary Examiner, Art Unit 1647